MORE THAN MEETS THE EYE:
THE EYE AND MIGRAINE

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Professor, Neurology, Ophthalmology
Disclosures:

- I am a part inventor on a patent pending on a thin film technology
- I am also a neuro-ophthalmologist

From Graham 1955
OBJECTIVES

1) To discuss the innervation of the eye in important to migraine

2) To discuss conditions that relate the eye and migraine

3) Consider treatment of eye-related conditions that may improve migraine
THAT THE EYE WOULD BE THE SOURCE OF PAIN IN HEADACHE and contribute to migraine IS NOT SURPRISING
Innervation of the Eye—

V1 Branches: lacrimal, frontal, nasociliary

V2: Zygomatic

Grant’s Atlas
The Cornea and the Dura are innervated by V1

Feindel, Penfield 1960
Cornea

- Most heavily sensory fibers in the body
- Can be visualized by confocal microscopy

Patel and McGhee, IOVS 2005; 46:4485-88
Cornea and Migraine?
Causes of Eye Pain from Ocular Causes—dry eye symptoms

- Dry eyes common—20-30% of population >45 yrs
- Symptoms NOT always low aqueous tear film production
- Can be associated with photophobia
- Abnormal corneal nerves
  - Chronic migraine?
Dry eyes ("tear film dysfunction") and migraine

- Sjogren’s increased incidence of migraine (46% of patients have migraine) (Pal Ann rheumat dis 1989; 48: 312-316)
- Recent study:

<table>
<thead>
<tr>
<th>migraine</th>
<th>control</th>
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Koktekit et al Cornea 2012; 31 1414-1416
Trigeminal innervation actively involved in tear film function
Eye pain increases migraine

• Clinical cases of eye pain in those with underlying migraine
  – (Friedman, Digre 2013; 53: 703-716)

• 15 patients with PRK and eye pain—all responded to sumatriptan (not sure how many started with migraine) (May et al Cephalalgia 2002; 22: 195-96)
Chronic Migraine Is Associated With Reduced Corneal Nerve Fiber Density and Symptoms of Dry Eye

Krista I. Kinard, MD; A. Gordon Smith, MD; J. Robinson Singleton, MD; Margaret K. Lessard, BS; Bradley J. Katz, MD, PhD; Judith E.A. Warner, MD; Alison V. Crum, MD; Mark D. Mifflin, MD; Kevin C. Brennan, MD; Kathleen B. Digre, MD

(Headache 2015;55:543-549)

<table>
<thead>
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<th></th>
<th>Chronic migraine</th>
<th>Controls</th>
<th>P</th>
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<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>14 Women/5 men</td>
<td>18 women/12 men</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>38.6</td>
<td>44.7</td>
<td>NS</td>
</tr>
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Dry eye questionnaire: all greater than 6 (consistent with dry eye) vs normal 2.7
Basal tear secretion, corneal sensitivity, tear film breakup time normal
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<tr>
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<th>Chronic migraine</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve fiber density</td>
<td>48.4 ± 23.5</td>
<td>71.0 ± 15</td>
<td>0.001</td>
</tr>
<tr>
<td>Nerve fiber length</td>
<td>21.5 ±11.8</td>
<td>26.8 ± 5.9</td>
<td>0.084</td>
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<tr>
<td>Nerve fiber branching</td>
<td>114.0 ± 92.4</td>
<td>118.1 ± 55.1</td>
<td>NS</td>
</tr>
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</table>
Dry eye/corneal nerve findings AND Chronic migraine

- Result of migraine process OR symptom leads to chronic migraine by continuous stimulation? OR a form of central sensitization?
- Treatment: artificial tears, topical cyclosporine, oral flaxseed oil, punctal occlusion
A cause of peripheral sensitization leading to central sensitization (corneal neuropathy?) vs Central sensitization leading to chronic pain OR both

Goadsby et al  NEJM  2002; 346:257

Rosenthal et al The Ocular surface 2009; 7:28-40
The Eye and Photophobia

• All of us have some threshold: e.g. matinee into bright light

• Light will decrease pain thresholds (in those with predispositions)—Kowacs Algometry study. Cephalalgia 2001; 21: 184-188.

• Seasonal changes (Vanagaite) lower threshold in winter, higher in summer Cephalalgia 1997; 17:733-741.
CAUSES OF PHOTOPHOBIA

EYE: ANTERIOR CAUSES
- Iritis; ocular inflammation
- Blepharitis, cyclitis; corneal inflammation
- Cataracts
- Corneal abrasion
- Corneal neuropathy

EYE: Posterior Causes
- Uveitis, Vitritis
- Retinal causes: Albinism, Achromatopsia, Retinitis Pigmentosa; rod/cone dystrophy
- Optic nerve: optic neuritis; papilledema; IIH

BRAIN CAUSES
- Meningitis: Meningeal irritation;
- Subarachnoid hemorrhage
- Pituitary apoplexy; hypophysitis
- Pituitary tumors
- Lymphoctic Choriomeningitis
- Pre-eclampsia

Other NEUROLOGICAL CONDITIONS
- MIGRAINE
- Blepharospasm
- Traumatic Brain Injury 55% Blast injuries!!
- Cyclic vomiting syndrome
- PSP

PSYCHIATRIC CONDITIONS
- Agoraphobia
- Depression
- Hang over headache
- Psychogenic

Other: Measles, Rabies, Trichinosis
Inflammatory Bowel Disease
Chediak-Higashi Syndrome
Ichthyosis follicularis with alopecia and photophobia (IFAP)
Trisomy 18

Fibromyalgia
Neurasthenia

Drugs: Barbiturates, Benzodiazepine, Chloroquine and acetazolamide,
Indinivar, methylphenidate
MIGRAINE

One of the major diagnostic criteria: photophobia, disability, nausea

80-90% of all patients have the symptom with migraine (Muellners et al 2001)

Some have the symptoms even interictally (Mulleners WM et al 2001)

In Chronic migraine, interictal photophobia exists (Lipton et al 2016)
Is there an anatomic basis for PHOTOPHOBIA?
Do you need vision?  NO

• 20 migraine patients with legal formed-vision blindness (6 NLP, 14 LP or better)
  NLP eyes no light sensitivity with migraine
  LP or better—all light sensitivity with attacks (Noseda et al *Nature Neuroscie*: 2010; 13:239-245)

• Evinger showed in mice—that sectioning the optic nerve did not alter the blinking or light
  sensitivity (*IOVS* 2011; 52:7852)
  – Could be due to associational cells to trigeminal ganglion?

• Iris may also have opsins –able to by-pass optic nerve entirely (Seko et al 2012)
Melanopsin pathway—non-visual pathway:
intrinsically photoactive retinal ganglion cells (iprgc)

Shown to be important in control of circadian rhythms and pupillary light response. (Non-visual photoreception)

• Peak of the melanopsin action spectrum for PLR is at 479 nm (blue spectrum). (dominant wave length at dawn and dusk)

• Animals with melanopsin who had disruption of rods/cones were light sensitive; animals without melanopsin were light insensitive (Hattar, et al Nature, 2003)

• In mice—a melanopsin antagonist that reverses light aversion! (Jones et al Nat Chem Biol. 2013 Oct;9(10):630-5)

First described 2003

Sparse dendrites
Large fields
Need more to get stimulated
Once turn on, hard to turn off
<table>
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<tr>
<th>Projection</th>
<th>Function</th>
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<tbody>
<tr>
<td><strong>SCN</strong> (supra chiasmatic nucleus)</td>
<td>Circadian rhythm</td>
</tr>
<tr>
<td><strong>IGN</strong> (intergeniculate leaflet)</td>
<td>Photic/non-photonic circadian clues</td>
</tr>
<tr>
<td><strong>OPN</strong> (olivary pretectal nucleus)</td>
<td>Pupillary light reflex</td>
</tr>
<tr>
<td>Para ventricular nucleus hypothalamus, LGN, interomedial cell column cervical cord, <strong>superior cervical ganglion</strong>, ventrolateral pre-optic nucleus</td>
<td>Multiple actions—circadian, non-visual perception; connections to sympathetics</td>
</tr>
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HOW DOES **discomfort** in PHOTOPHOBIA OCCUR?

Need trigeminal connections
Does Melanopsin co-locate with the trigeminal system?

**YES**

A neural mechanism for exacerbation of headache by light

Rodrigo Noseda¹, Vanessa Kainz¹, Moshe Jakubowski¹, Joshua J Gooley², Clifford B Saper²,³, Kathleen Digre⁴ & Rami Burstein¹,³

The perception of migraine headache, which is mediated by nociceptive signals transmitted from the cranial dura mater to the brain, is uniquely exacerbated by exposure to light. We found that exacerbation of migraine headache by light is prevalent among blind individuals who maintain non–image-forming photoregulation in the face of massive rod/cone degeneration. Using single-unit recording and neural tract tracing in the rat, we identified dura-sensitive neurons in the posterior thalamus whose activity was distinctly modulated by light and whose axons projected extensively across layers I–V of somatosensory, visual and associative cortices. The cell bodies and dendrites of such dura/light-sensitive neurons were apposed by axons originating from retinal ganglion cells (RGCs), predominantly from intrinsically photosensitive RGCs, the principle conduit of non–image-forming photoregulation. We propose that photoregulation of migraine headache is exerted by a non–image-forming retinal pathway that modulates the activity of dura-sensitive thalamocortical neurons.

1) Linked trigeminal system to melanopsin pathway and visual pathway
2) Projected to the Somatosensory Cortex AND occipital cortex

*Nature NEUROSCIENCE* 2010; 13:239-245

- Newborn mice—only ipRGC active up to post natal day 9
- Light produced vocalizations similar to distress from isolation from litter or noxious stimuli (melanopsin knock out mice did not exhibit aversive behavior)
- Early gene produces Fos in posterior thalamus AND light induced activation of amygdala.

Delwig et al 2012; PLOS one 7 e43787
TREATMENT of PHOTOPHOBIA

• None
• Dilation of an acutely inflamed eye
• Treat underlying neurological/psychiatric conditions: migraine, meningitis, depression, anxiety etc
• Reduce dark adaptation (those in the dark need to slowly come to the light)
• Tinted lenses
  – Gray
  – FL-41 (Good, Headache 533-536, 1991)
  – Red contact lenses in photophobia for cone disorders (Park AJO 2004;137:774-5)
We found **FL-41 block blue light** decreases light sensitivity in patients with migraine and blepharospasm

First used in orphanages in England in migraine patients to reduce symptoms (Good, et al Headache 1991; 31: 533-536)

**FL-41 Tint Improves Blink Frequency, Light Sensitivity, and Functional Limitations in Patients with Benign Essential Blepharospasm**

Hogan, Subhash, Blair, Katz et al Thin film filter spectacle coatings for migraine and photophobia J Clin Neuroscience 2016; Feb 27 Epub ahead of print

**Blocks 480 nm light (melanopsin)**
Approach to Diagnosis of Photophobia

- Careful history and examination
- Look for migraine (pain, nausea)
- Look for tear film dysfunction—tear film, tear film breakup time, corneal staining
  - Corneal neuropathy: lidocaine eye drops
- Blepharospasm—can be “reflexive” to light
- Consider screening for depression and anxiety
Is there evidence on history or physical examination of central process?

Yes

Evaluate with neuroimaging, lumbar puncture and laboratory studies

No

SLE: dry eyes, iritis, uveitis, corneal staining, Shirmer test: +

Yes

Treat dry eyes, anterior segment disease: lid hygiene, ointments, artificial tears, anti-inflammatory drugs

No

Does the photophobia resolve with topical anesthetic or dilation?

Yes

Look for corneal neuropathy, iritis, cyclitis, uveitis, dry eyes

No

History of hemeralopia, nyctalopia, decreased visual acuity

Yes

Retinal dystrophy: family history, electrophysiologic studies, genetic testing

No

Evidence of excessive blinking, involuntary eye closure to light?

Yes

Treat blepharospasm: botulinum toxin, medications, surgical myectomy

No

Migraine history: HA, eye pain, phonophobia, nausea, vomiting

Yes

Treat migraine; screen for anxiety, depression

No

From Digre KB, Brennan KC. Shedding Light on Photophobia JNO 2012; 32:68-81
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OTHER TREATMENTS

• TREAT DRY EYES (lubrication, lid hygiene, gabapentin drops; serum tears; etc)
• Treat underlying migraine, blepharospasm
• Botulinum toxin  (Shoari M, Katz BJ Neuro-ophthalmology 31: 105-110; Belliveau, Jordon J Neuro-ophthalmol 2012; 32: 293)
• Anti-convulsants (gabapentin) (anecdotal)
• Melatonin (anecdotal)
• Treat underlying depression and anxiety
• Consider a sympathetic block
Migraine and the EYE

- **Photophobia**: probably every patient has a reason—the cornea (dryness; corneal neuropathy, trigeminal dysfunction), plays a role in migraine AND blepharospasm

- Dry eye studies/treatments may help us modulate migraine

- **FL-41 tint** seems to be helpful in reducing some of the symptoms of photophobia in migraine

- We need more treatments for dry eye, eye pain and photophobia, and chronic migraine!
Collaborators

• Wesley H. Adams, MD*
• Rebecca Judd, MD*
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• Marcus Blackburn MD*
• Randall Lamb MD*
• Thomas Buchanan MD
• Stephanie Llop MD*
• Jonathan Frandsen MD*
• Krista Kinard MD
• Laura Hanson MD

• Bradley J. Katz, MD, PHD
• Judith Warner, MD
• Gordon Smith MD
• KC Brennan MD

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